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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/689,550	10/21/2003	Pnina Fishman	FISHMAN10A	9316

1444 7590 11/15/2006

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EXAMINER	
SANG, HONG	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/689,550	FISHMAN ET AL.	
	Examiner	Art Unit	
	Hong Sang	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-7 and 9-19* is/are pending in the application.

4a) Of the above claim(s) *6,11,14,15 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7,9,10,12,13 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RE: Fishman et al.

1. Applicant's response filed on 9/20/2006 is acknowledged. Claims 1, 2, 4-7, 9-19 are pending. Claim 3, and 8 are cancelled. Claims 6, 11, 14, 15 and 19 are withdrawn from further consideration. Claims 1, 4, 6, 7, 9, 11, 16, 18 and 19 are amended.

2. Claims 1, 2, 4, 5, 7, 9, 10, 12, 13 and 16-18 are under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections Withdrawn

4. The objections to the specification because the first line of the specification is not updated to reference the earlier filed applications is withdrawn in view of applicant's submission of a substitute applicant data sheet.

Rejections Withdrawn

5. The rejection of claims 3 and 8 under 35 U.S.C. 112, second paragraph, as being indefinite for reciting the term "a proliferative-related disease state" and "proliferative disease state" is withdrawn in view of applicant's cancellation of the claims.

6. The rejection of claims 1-5, 7-10, 12, 13 and 16-18 under 35 U.S.C. 102(a) as being anticipated by Madi et al.(Drug Dev. Res., 2002, May 56(4): 560, IDS) in view of the teaching of Wei et al. (US Patent No. 6,063,376, Date of Paten 5/16/2000) and

Keyomarsi et al. (US Patent No. 5,543,291, Date of Patent 8/6/1996) is withdrawn in view of applicants submission of Declaration under 37 CFR § 1.132 showing that the article describes applicant's own work.

7. The provisional rejection of claims 1, 2, 7, 12, 13, 16 and 17 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5 and 15 of copending Application No. 10/565,238 is withdrawn in view of applicants amendment to claims to limit the disease state to proliferative-related disease state that is a tumor or psoriasis.

Response to Arguments

8. The rejection of claim 1-3, 7, 8, 12, 13, 16 and 17 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a tumor in a subject, a method for determining the severity of a tumor in a subject and a method for determining whether a subject has a high probability of responding to a therapeutic treatment of a tumor comprising detecting the level of expression of A3AR in said tumor cells, does not reasonably provide enablement for a method of detecting any and all disease state in a subject, a method for determining the severity of any and all disease state in a subject and a method for determining whether a subject has a high probability of responding to a therapeutic treatment of any and all disease state comprising detecting the level of expression of A3AR, or A3AR protein fragment in a sample of cells suspected of being in the disease state is maintained.

Applicants amended claims to limit the proliferative-related disease state to tumor or psoriasis. The response states that as the specification is enabled for tumors, there is no reason to believe that the present invention would not also be operable for psoriasis.

Applicant's arguments have been carefully considered but are not found persuasive. The amendment to the claims to limit the proliferative-related disease state to tumor or psoriasis cannot overcome the instant rejection. As indicated in the previous office action, up to date the art only teaches that A3AR is overexpressed in certain cancers such as melanoma, and lymphoma. Fishman et al. (Curr. Topics Med. Chem. 2003, 3: 463-469, IDS) teach that A3AR expression level is found to be low in most body tissues other than testis, eosinophiles, basophils and neutrophils which all demonstrated massive expression (see page 463, left column, last paragraph). Fishman et al. teach that tumor cells such as human A375, melanoma, human Jurkat T cell lymphoma and murine pineal tumor cells, significantly express A3AR (see page 463, right column). Fishman et al. teach that activation of A3AR evokes different downstream signal transduction pathways which are cell type dependent and may attribute to the diverse responses (see page 463, last paragraph). Fishman et al. teach that there is a debate in the literature regarding the pro or anti-inflammatory response medicated via A3AR activation in these cells; some reports recommend activating A3AR to block the inflammatory response while others favor the implementation of A3AR antagonists for the very same purpose (see page 464, left column, 4th paragraph). Therefore, the role that A3AR plays in different diseases is unpredictable. Moreover,

activation of a receptor does not always correlate with the overexpression of a receptor. While the art indicates that A3AR plays an important role in various physiological processes, it does not teach the A3AR is overexpressed in psoriasis. The instant specification teaches that A3AR is differentially expressed in certain tumor cells compared to normal cells. However, there is no indication that overexpression of A3AR is correlated with psoriasis: As such, one of ordinary skill in the art would reasonably conclude that the specification has not enabled the method for detection of psoriasis, the method for determining the severity of psoriasis and a method for determining whether a subject has a high probability of responding to a therapeutic treatment of psoriasis comprising detecting the level of expression of A3AR or A3AR protein fragment. Furthermore, as indicated in the previous office action, the "A3AR protein fragment" recited in claims 12 and 13, for example, which encompasses fragments that are as small as 2 amino acid residues, most likely would not function as the A3AR protein. Detection of the "A3AR protein fragment" in a cell would not all represent the actual expression level of the A3AR protein. Because of these reasons, the rejection is maintained.

9. The rejection of claims 1-5, 7-10, 12, 13 and 16-18 under 35 U.S.C. 103(a) as being unpatentable over Baraldi et al. (US Patent No. 6,407,236B1, Data of Patent: 6/18/2002, earliest effective filing date at least 8/23/1999) in view of the teaching of Reeves et al. (Inflamm. Res. 2000, 49:666-672), Wei et al. (US Patent No. 6,063,376,

Date of Paten 5/16/2000) and Keyomarsi et al. (US Patent No. 5,543,291, Date of Patent 8/6/1996) is maintained.

The response states that Baraldi discloses compounds endowed with selective A3 adenosine receptor agonist activity, and suggests that the compounds may be used in the detection and/or treatment of cancer (column 14, lines 31-34). Baraldi further states that tumor cells have been shown to express the A3 receptor (column 14, lines 32-34; column 15, lines 8-16), and shows the characterization of A3 receptors in some human tumor cell lines (example 18, column 39). However, the A3 receptor appears on many types of cells and fulfills a variety of functions, as taught by Baraldi (column 1, lines 37-50). Nowhere does Baraldi teach the expression of A3AR in normal cells nor the differential expression of A3AR on cancerous as compared to normal cells. Therefore, Baraldi does not teach a method for determining the presence of tumor cells among normal cells, but rather a method for determining the presence of the A3 receptor on cells, which are already known to be tumor cells. The present application on the other hand, provide examples demonstrating A3AR protein expression in a number of tumor cell types as compared to normal cells. These include colon carcinoma cells (examples 1-4), breast cancer cells (examples 2, 3, 4) and melanoma cells (example 5). This is not at all taught by Baraldi. Reeves does not cure the deficiencies of Baraldi as Reeves merely discloses A3 anti-peptide anti-sera. Wei suggests a diagnostic assay for detecting altered levels of hdCK2 protein in various tissues as compared to normal control tissue samples to detect the presence of a disease and Keyomarsi discloses correlation of cycline E protein aberration to different

stages of breast cancer. However, neither Wei nor Keyomarsi teach anything about the use of A3AR to detect tumor cells in a subject. Accordingly, no combination of Baraldi, Reeves, Wei and Keyomarsi make obvious the processes of the present invention.

Applicant's arguments have been carefully considered but are not found persuasive. Baraldi et al. claim a method for determining the presence of tumor cells which possess a high concentration of adenosine A3 receptors in a patient or in a cell sample, and a method of determining the presence of residual tumor cells which possess a high concentration of adenosine A3 receptors following surgical removal of a tumor, comprising administering to the patient or to the sample a compound which includes a radiolabel or fluorescent label which can be detected following binding of the compound to tumor cells, allowing the compound to bind to tumor cells and detecting the radiolabel (see claims 38-43), wherein the compound selectively binds A3AR (see column 1, last paragraph, column 5, lines 7-10). While Baraldi et al. do not expressly teach comparing the expression of A3AR in tumor cells to that in normal cells, because the method is directed to *in vivo* determining the presence of tumor cells which possess a high concentration of A3AR in a subject and *in vivo* determining the presence of residual tumor cells which possess a high concentration of A3AR following surgical removal of a tumor (see claims 38-41), the method would comprise a step of comparing the expression of A3AR in tumor cells to that in normal cells or surrounding tissues in order to detect and differentiate the labeled tumor cells or residual tumor cells from surrounding cells or tissue. Moreover, contrary to applicant's assertions that Baraldi et al. teach that the A3 receptor appears on many types of cells and fulfills a variety of

functions (column 1, lines 37-50), Baraldi et al. only states "the A3 selective receptor mediates processes of inflammation, hypotension, and mast cell degranulation. This receptor apparently has a role in the central nervous system" (see column 1, lines 37-50). These teachings do not indicate that A3AR is not differentially expressed in cancer cells vs. normal cells and that A3AR would not be useful for cancer detection. In fact, Baraldi et al. claim a method of *in vivo* and *in vitro* detecting tumor cells. While Baraldi et al. do not teach comparing the level of the expression of A3AR to the values of the calibration curve, these deficiencies are made up for in the teaching of Wei. Wei et al. teach a method of determining the amount of the protein present in a given volume of patient sample by comparing against a standard curve (see column 10, lines 40-42). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure the level of the expression of A3AR protein and thereafter detect a tumor or determine the severity of a tumor by comparing the level of the expression of A3AR protein to a normal control tissue or to a standard curve in view of the teaching of Baraldi, Reeves. Wei and Keyomarsi. Because of these reasons, the rejection is maintained.

Conclusion

10. No claims are allowed

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11: Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hong Sang, Ph.D.
Art Unit 1643
Oct. 31, 2006

CHRISTOPHER H. YAEN
PRIMARY EXAMINER